Neuroethics for Novel Neurotechnologies

Collaborative webinar

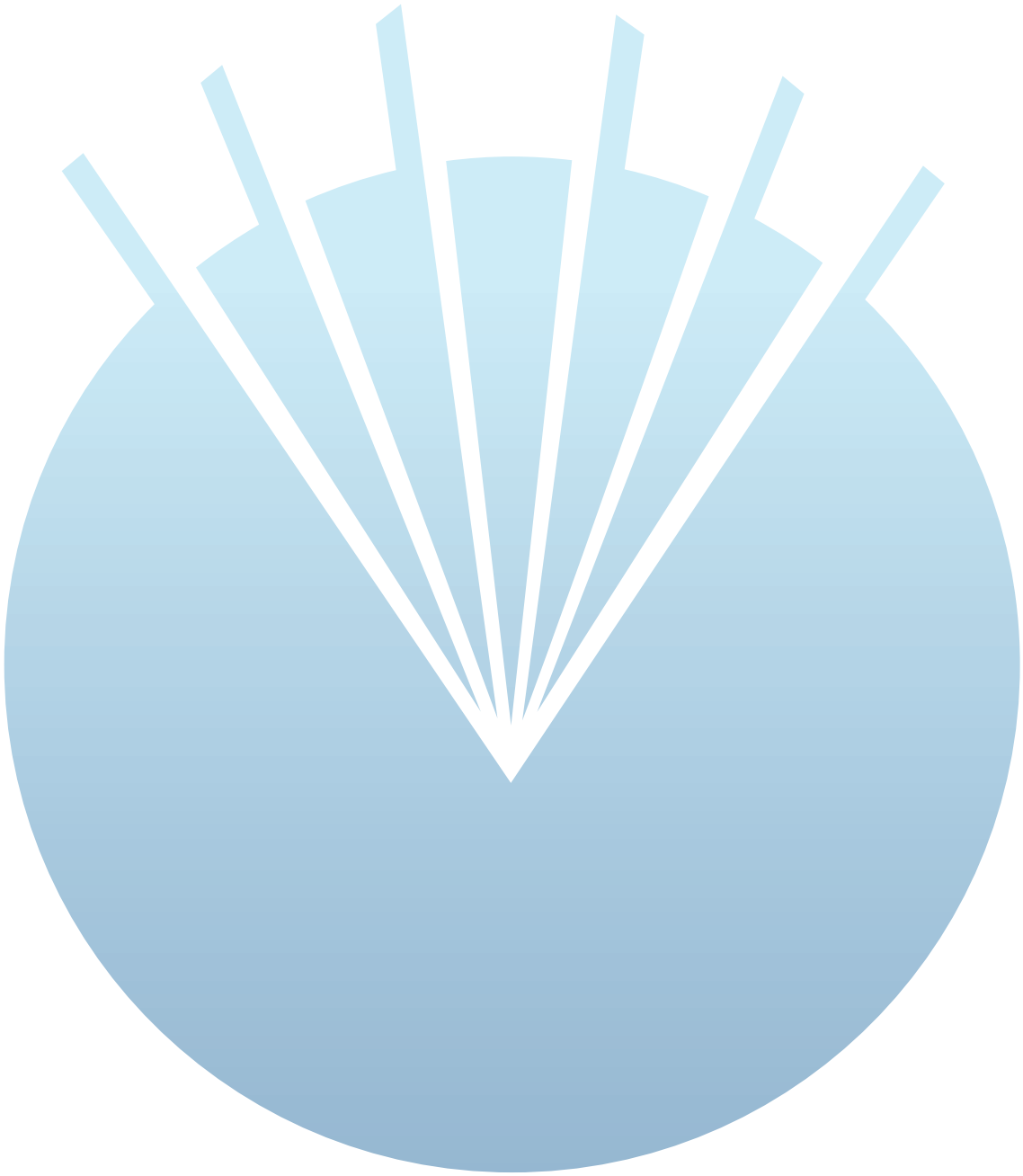
19 April 2021

3–4:30 pm ET

Sponsored by

Focused Ultrasound Foundation

Pan-Canadian Neurotechnology Ethics Consortium



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Executive Summary

This white paper summarizes a 90-minute webinar titled "Neuroethics for Novel Neurotechnologies" that was organized by the Focused Ultrasound Foundation and the Pan-Canadian Neurotechnology Ethics Consortium (PCNEC) on April 19, 2021.

The goal of the webinar was to describe how scientific progress in the advancement of neurotechnologies, from preclinical experimentation to real-world treatments, creates ethical questions of readiness, equitable patient access, and legal and intellectual property rights.

Nir Lipsman, MD, PhD, set the stage by describing the urgent need to develop novel treatments and better understand what drives these conditions as brain disease has become more common, accounting for a larger portion of human morbidity and mortality. In parallel, there is an essential need to critically evaluate *how* researchers investigate these new treatments and the associated ethical ramifications. Because it is essential to put ethical questions in the appropriate broader context, the field of neuroethics has blossomed over the past 20 years, addressing the questions at the interface of brain function and technology. We must engage in important ethical discussions to prepare the field, physicians, and ultimately the patients, for these changes.

Judy Illes, PhD, described the neuroethics field's efforts to proactively align solutions to thorny, challenging, ethical problems that accompany discoveries in neuroscience. This webinar was designed to challenge colleagues to consider neurotechnology and its implications for people and societies around the world.

Three experts presented background information on vulnerable populations, placebo effects, and selected regulatory issues. Specifically, **Patrick McDonald, MD**, described vulnerable populations, including people who enroll in clinical trials or agree to undergo novel treatments. **Matthew Burke, MD**, shared the importance of studying and analyzing placebo effects in neurotechnology trials. **Jennifer Chandler, LLB, LLM**, described regulatory issues that raise ethical concerns, introducing concepts from device regulation, clinical regulation, and patient access. **Helen Mayberg, MD**, delivered the plenary presentation, "DBS for Depression: A Case Study. The Neuroethics of Changing Expectations." She stated that scientists must manage their expectations—and those of their patients (i.e., research subjects)—or problems will persist as novel and unknown neurotechnologies advance.

A lively panel discussion then engaged all presenters and revealed some common themes, such as:

1. providing patient access to novel treatments while creating an environment of shared decision making without unrealistically raising expectations;
2. justifying the costs of obtaining neuromodulation data in the process of seeking data that are sufficiently impactful to make a difference in patients' day-to-day lives; and
3. envisioning the future of neuroscience and modulatory techniques outside of the realm of open access, especially regarding access to patient data.

The Foundation intends to keep ethical issues, and all issues related to the development of focused ultrasound as a noninvasive, life-saving therapeutic technology, at the forefront of the community conversation. Doing so is part of the Foundation's mission to overcome the numerous technological, economic, regulatory, and reimbursement obstacles that exist.

The link to **view the webinar** can be found on the Foundation's website.

Welcome, Introductions, and Background Information

Jessica Foley, PhD, welcomed attendees, provided logistical information for asking questions during the discussion, and introduced Dr. Lipsman and Dr. Illes as the webinar co-hosts.

Dr. Lipsman explained that he was presenting from the traditional territory of many nations, including the Mississaugas of the Credit, the Anishnabeg, the Chippewa, the Haudenosaunee, and the Wendat peoples. He acknowledged this territory to show recognition and respect for Aboriginal Peoples as part of ongoing efforts to build healthy, reciprocal relations, the keys for reconciliation.[1] Setting the stage for the webinar, Dr. Lipsman highlighted the outstanding roster of presenters, including plenary presenter Dr. Mayberg, and stated that the fields of focused ultrasound and neuroscience are at an inflection point. As the understanding of the brain continues to grow and evolve, so does the ability to intervene with advances in imaging technology hardware and software. As brain disease has become more common, accounting for a larger portion of human morbidity and mortality, there is an urgent need to develop novel treatments and better understand what drives these conditions. In parallel, there is an essential need to critically evaluate how researchers investigate new treatments and the associated ethical ramifications. Because it is essential to put ethical questions in the appropriate broader context, the field of neuroethics has blossomed over the past 20 years, addressing the questions at the interface of brain function and technology. The research community needs to prepare the field, and ultimately the patients, for these changes. Toward this end, the PCNEC is a think tank of scholars spanning the neurosciences that was formed to identify key questions in the field and anticipate ethical issues in neurotechnology. Dr. Lipsman encouraged attendees to join him and the other presenters in charting new ground in this field.

Dr. Illes explained that she has been privileged to conduct and share her work from land in the unceded territories of the Musqueam, Squamish, and Tsleil-Waututh people in Vancouver, British Columbia. Dr. Illes said that the field of neuroethics aims to proactively align solutions to thorny, challenging, ethical problems that accompany discoveries in neuroscience, so this webinar was designed to challenge colleagues to consider neurotechnology and its implications for people and societies around the world. Dr. Illes invited attendees who were inspired or who had additional questions to become involved in PCNEC, a Canadian-led initiative that embraces the international global community of doctors, ethicists, scholars, patients, policymakers, industry, and others. PCNEC seeks to learn how it can move the global community forward on the ethical, legal, and social implications of functional neurosurgery. Dr. Illes thanked the Focused Ultrasound Foundation for supporting PCNEC in this important endeavor.

Presentations

To provide an overview of the topic and set the stage for the panel discussion, the webinar included three recorded presentations and one live plenary presentation.

Vulnerable Populations

Dr. McDonald delineated that neurosurgery research and clinical care is, by definition, conducted almost entirely on vulnerable populations. Vulnerability, which is addressed in many codes of ethics, is defined in several ways, with Dr. McDonald's preferred definition encompassing a variety of concepts: "The quality or state of being exposed to the possibility of being attacked or harmed, either physically or emotionally," "circumstances wherein the established checks and balances of power and interest are no longer sufficient in promoting the just treatment of persons," and "those that experience adverse health care outcomes compared with the general population by virtue of both internal and external factors."[2–4] Most citations in the ethics literature about vulnerable populations appear in the context of medical research. Although the United States' National Institutes of Health has identified prisoners, pregnant women, children, neonates, and human fetuses as populations that require additional protections and the Canadian Institutes of Health Research states that vulnerable populations have "a diminished ability to fully safeguard their interests in the context of a specific research project,"[5] Dr. McDonald said that the vast majority of encounters with vulnerable populations take place in the day-to-day clinical care environment, outside the research context.

Although not all-encompassing, PCNEC considers the following groups of people as vulnerable populations:

- People with psychiatric illnesses
- Children
- People with disorders of consciousness or capacity
- First Nations, Inuit, and Metis persons
- People with socioeconomic vulnerability due to poverty, lack of education, living in disadvantaged geographic regions or racialized communities, or identifying as lesbian, gay, bisexual, transgender, queer, or two-spirited

The 2019 coronavirus pandemic revealed many disparities among vulnerable populations. Dr. McDonald shared an example from the racialized and poor neighborhood in Toronto where he grew up that shows a high rate of infection and an incredibly low vaccination rate relative to wealthier neighborhoods in Toronto. This type of disparity is also seen in

access to neurotechnologies; for example, studies show the African American community, Medicaid beneficiaries, and people who live in certain geographic regions have different access to deep brain stimulation (DBS) compared to patients from other races and socioeconomic backgrounds.[6,7] In the research context, the risks and benefits may be more fairly distributed; however, after neurotechnologies become widely available and accepted in the medical community, research and medical communities must play a critical role in ensuring that access does not depend on educational status, income, or geography. Patients who need neurotechnologies tend to not only be refractory to treatment, but also suffer from illnesses that, by definition, often lead to vulnerability. Care must also be taken to ensure that the therapeutic misconception is minimized in these populations. Canada is a vast country with significant urban and rural divides in access to healthcare. Going forward, we need to ensure that participation in research as well as access to proven neurotechnologies is not dictated by where a patient resides.

It is critical that First Nations, Inuit, and Metis people and other underrepresented populations are central to the neuroethics discussion by using a vigorous patient or caregiver engagement process at the early stages of an investigation. Another strategy is for researchers to engage patients and advocacy groups when planning and prioritizing their work and clinical trials.

Placebo Effects and Neurotechnologies

As the placebo effects co-lead for PCNEC, **Matthew Burke, MD**, said that placebo effects are highly relevant when studying new neurotechnologies. While completing his cognitive neurology fellowship in transcranial magnetic stimulation (TMS), Dr. Burke reviewed studies on clinical applications of TMS and was struck by the fact that many trials had a large and notable active group response *and* a large placebo group response. For example, one depression treatment trial had a 37% remission rate of depression in the sham group alone.[8] Although many TMS trials for depression reported similar results, there has been limited attention paid to the placebo responses.

Dr. Burke stressed that researchers need to analyze, understand, and interrogate the data on placebo effects. For example, a TMS stroke treatment study described a two-thirds sham group response rate on the Fugl-Meyer Assessment of Motor Recovery after Stroke.[9] The investigators could not explain this response and decided that there must have been an active influence in the sham group. They conducted another trial with a different sham group and found similar results.[10]

Although important for neurotechnologies, the placebo effect is rarely the topic of conversation or study. The medical field tends to view the placebo effect as a negative, rather than an opportunity to explore, understand, and potentially leverage.[11] Dr. Burke joined Dr. Ted Kaptchuk's **Program in Placebo Studies and the Therapeutic Encounter** at Harvard University, which helped him understand that placebo effects involve a complex interaction between internal and external cues. He said that placebo effects can be defined as the beneficial effects surrounding the context rather than the treatment itself. [12,13]

These effects might be due to caregiver interactions or care provider interactions, expectations, and emotions.

Dr. Burke said that the keynote presenter, Dr. Mayberg, has conducted important and seminal studies on understanding placebo effects in the brain.[14] She has shown that certain areas of the brain become activated or deactivated with a placebo effect—similar to an antidepressant effect. This critical and rapidly evolving work has been important to many fields, including the study of Parkinson's disease. Recent models have shown network changes that happen in the brain in response to placebo effects. What might be underlying some of those brain region and network changes is an entire topic on its own. Briefly, it may be from positive expectations, reduction of anxiety, or activation of reward centers.[15]

Regarding clinical research, the placebo response is the overall response in the placebo group, but the response is not due solely to placebo effects; other effects at play are important to delineate. Many factors can affect the magnitude of the placebo effect. For example, an early hypertension clinical trial with four treatment arms and two placebo groups found an intravenous placebo to be more effective than a pill placebo in reducing hypertension.[16] This finding spurred broad community discussion about the placebo effect and the intensiveness of treatment. The only way to truly separate placebo effects from the effects of time, participant in a clinical trial, observations, and more is to have a no-treatment control group. Unfortunately, no-treatment control groups are rarely included in clinical studies.

Because brain stimulation technologies are elaborate and exciting, the placebo effect and many related study design factors must be considered. For example, appropriate and adequate blinding is critical. A sham device that mimics the active device should be used, and all parameters must ensure that patients cannot tell the difference between the two. Avoiding meaningful stimulation of the brain with a sham device is not trivial. Sham devices are in development for a variety of different technologies. Blinding validity is another critical measure. Trials can be designed to exclude high placebo responders, which is a controversial topic. Chosen outcome measures may also be impacted differently by placebo effects. For example, an article on asthma published by Ted Kaptchuk's group shows almost no placebo effect with an objective outcome measure, but a very large placebo effect for the subjective feeling of shortness of breath.[17] It is especially critical to think about outcome measures in fields where high placebo effects are likely. Interpreting efficacy can be overly complicated in this context, and a hypothetical example can be posed. A drug trial with a high specific effect and a modest placebo effect with sufficient enrollment numbers receives regulatory approval. A large device trial with a placebo effect and more modest specific effect would be deemed ineffective and not gain regulatory approval; but calculating the absolute improvement of the patient would make it difficult to argue that the device was at least as beneficial (if not superior) to the drug. Now when that drug is not available or produces side effects, it raises several interesting philosophical and ethical questions.

Researchers and clinicians may be able to improve patient outcomes by leveraging placebo effects and learning from large responses. Dr. Burke encouraged neurotechnology

researchers to try to understand placebo effects and to think about the ethical implications of developing neurotechnologies. Many concepts are ripe for consideration, such as whether deception can ever be justified, because some placebo studies may require a level of deception or incomplete information at the time of informed consent.

Selected Regulatory Issues

Ms. Chandler described four types of neuroethical regulatory issues: device regulation, clinical regulation, access, and intellectual property.

A key issue for novel neurotechnologies will be the nature of regulatory requirements that may apply to design, manufacturing, distribution, and use. Device regulation includes not just regulatory requirements set by national regulators like the U.S. Food and Drug Administration (FDA), which licenses medical devices. Various engineering standards and consensus guidelines by entities like the **Institute of Electrical and Electronics Engineers**, the **Brain-Computer Interface Society**, and the **Organisation for Economic Co-operation and Development** provide information about the legal standard of care that will be expected of those commercializing neurotechnologies. When new technologies emerge, such as focused ultrasound, the various regulatory bodies ask questions about how the new modality should be regulated. Each device's design standards inform the answers to regulation and legal product liability questions. A recent example is the FDA's efforts to determine what might be best practices for the therapeutic use of virtual and augmented reality. Another relevant domain of regulation has to do with the regulation of human subjects research during the development of novel neurotechnologies. What are the sponsor's post-trial responsibilities to participants in invasive device trials? Do sponsors have an obligation to cover the costs for explantation of a device, to supply replacement batteries, or to facilitate continued access? If sponsors do not pay, who is responsible for these ongoing costs? Should the researchers be responsible? What about publicly funded healthcare systems or privately funded insurance companies?

Clinical regulation refers to the legal and regulatory structures governing clinical practice. Relevant here are laws that regulate neurotechnological interventions and neurosurgery for psychiatric disorders (NPD). Recent consensus guidelines were published on the topic, and there has been comment from the field that laws rather than guidelines are required. A paper published in 2021 examined a selection of the existing laws from a range of jurisdictions around the world that govern NPD.[18–20] The definition of NPD varies widely and can be quite broad. For example, Queensland, Australia, has rules related to nonablative neurosurgical procedures, which are defined as surgery on the brain that does not cause deliberative damage for the treatment of mental illness. These procedures could conceivably include wide-ranging forms of intervention. Regulation of DBS differs across the world, but is sometimes captured by laws on NPD, and Scotland specifically regulates TMS. Many technology-specific and indication-specific laws exist around the world. Further, more general laws apply to all clinical interventions and will therefore apply to the clinical use of new and emerging treatments.

Access issues involve costs, funding, and the accessibility to the patient of the technology, and these are considerations that often interact with regulatory issues. For example, an article published by PCNEC member Zelma Kiss, MD, PhD, raised the issue of how the regulatory approval of a new device that had a shortened battery life but without evidence of therapeutic improvement led physicians to switch to more expensive rechargeable devices to avoid exposing their patients to repeated surgeries for battery replacement.[21] This switch to a more expensive device effectively decreased availability to patients within a context of limited resources (whether publicly or privately funded through insurance). Another example is the exclusion of patients with cognitive impairments from certain forms of long-term DBS therapy. These examples raise questions about human rights laws and access to treatments. Medical tourism occurs when a person travels to another country to seek medical care, and this may also raise access issues. For brain interventions, medical tourism is driven by both technology availability and cost in a jurisdiction. For example, DBS is widely advertised online to medical tourists in high-cost jurisdictions, which raises regulatory concerns when people are exposed to unsafe treatments or experience difficulties, the cost of which must be assumed by the domestic system when patients return home. Medical tourism also raises issues about displacement of care in the destination jurisdictions where people seek these treatments.

Intellectual property is the domain of law that includes patents and copyrights, among other things. PCNEC members have been investigating the number of method patents filed for stimulation or neuromodulation of specific brain regions for certain conditions.[22–24] Their concern lies with the accumulation of overly broad patents that might impede further development or research in the area—or the development of other products. Overly broad patenting is reflected in the saga of genetics and BRCA gene patents. Researchers are raising questions about the breadth of neurotechnology patents that are being offered as well as whether specific brain zones should be eligible for method patents. Another issue is the impact of copyrights for neurotechnology software end-user license agreements (EULAs). EULAs fall under copyright law, which governs the use of software that is integrated within a closed-loop implantable medical device or within programming devices for implanted medical devices. EULAs are not usually available to patients, because they typically go to the hospital or the clinician performing the implant. However, EULAs often include limitations on software reverse engineering, decompilation and disassembly, disclaimers of warranty, waivers of liability, and sometimes a consent to the collection and use of data. Patients should have access to the algorithms for closed-loop forms of implanted medical devices, especially for adaptive, closed-loop devices that impact cognitive function. So, a key question for the future is: What forms of restrictions are appropriate to recognize and permit within copyrighted license agreements that are embedded in medical devices?

DBS for Depression: A Case Study
The Neuroethics of Changing Expectations

Helen Mayberg, MD, described the changing expectations around the use of DBS to treat depression. She stated that scientists must manage their expectations—and those of their patients (i.e., research subjects)—or problems will persist as novel and unknown neurotechnologies advance. Dr. Mayberg disclosed her industry affiliations and said that her initial work in Toronto led to a patent submission, as described by Ms. Chandler. She noted her willingness to discuss the ethical considerations for this type of patent during the Q&A session.

Dr. Mayberg explained that although neuromodulation is used to treat many neural circuit disorders (e.g., movement disorders, obsessive-compulsive disorder, seizure disorders, addictive disorders), she would use an example from treating depression in her presentation. She asked whether understanding the fundamental biology and using scientific advances could reduce highly complex neuropsychiatric disorders to fundamental principles and targets that could be poked, stimulated, blocked, or enhanced to treat these disorders. When researchers and physicians use a novel, noninvasive device or an intermediate device such as focused ultrasound to modulate an illness circuit, they have an obligation to understand **why** it is needed, **where** to stimulate, **what** should happen, and **who** is eligible to receive the treatment. Researchers should determine whether circuits can be safely and effectively modulated. These pragmatic issues must be addressed with every new technology and every new indication. An ethical consideration occurs when the mismatch of expectation meets reality. Targets must be matched to a disease, a syndrome, a symptom, and each patient, and personalized approaches that optimize response must be devised for each patient. Vulnerable populations—including treatment-resistant patients—and patient access are also ethical issues. These pillars are true for DBS and all types of invasive and noninvasive procedures.

The patient must remain at the center of the discussion. Listening to patients and asking them to describe their experiences is essential for understanding what they want to change by undergoing treatment. Depression is not an episodic problem; it is an all-enveloping state: The brain can hijack every aspect of life, including moving and thinking. Patients describe feeling paralyzed; some say that being unable to accomplish daily tasks changes their identity. This combination of behavioral elements defies simple brain organization. Patients can provide a first-person perspective to describe their recovery goals for relieving pain, moving, and restoring function.

Researchers should set the bar for new depression treatments. With depression, by the time a patient has had five episodes, even if they have recovered previously, the likelihood of another recovery decreases to almost immeasurable levels. The possibility that a new neurotechnology will be beneficial is a bold assumption based on the evidence; however, the question becomes one of safety with a justifiable rationale. There are only three newly approved treatments for depression (vagus nerve stimulation, repetitive TMS, and ketamine), but none is reliable or systematically tested in patients who have failed electroconvulsive therapy. This group of patients, which is not the majority of patients with depression, is the focus of Dr. Mayberg's attention.

Dr. Mayberg's approach to DBS has led to a remarkable and sustained treatment effect in many patients. Targeting an area in the subcallosal cingulate with high-frequency stimulation in a small cohort of people who have been continually studied over 12 years has shown a sustained positive response. The pilot cohort was treated in Toronto, and the study was replicated in Atlanta with 28 patients. The technology is advancing, and other targets and parameters are yielding interesting results. An eventual goal is to scale the treatment to reach more patients. Dr. Mayberg envisions a future when patients receive individual, or personalized, implants that can interrupt moods by reading brain signals. Several alternate studies with predefined and individualized targets and various parameters are under way to determine the best designs and help researchers make evidence-based decisions to set their research priorities.

In her studies of the subcallosal cingulate, recovery from depression is not linear; it usually involves an acute response followed by continued progressive improvement over time. Technologically, work is now ongoing to develop new metrics to better characterize this time course and its neural correlates. Ethically, physicians need to help patients reframe their expectations for recovery to consider these acute and delayed responses to treatment. Everyone has a different experience. The initial effect may be predictable based on studies, and the experiences might be similar, but treatment responses and time courses are not identical. This variable response rate warrants further scientific study. Biomarkers, brain signal readouts, and behavioral responses are all a part of the data and needed for risk mitigation.

Several new studies for treatment-resistant depression are under way, with some exploring strategies using closed-loop technologies where stimulation parameters are developed based on readouts taken directly from the brain. In Dr. Mayberg's studies, patients receive continuous brain stimulation as before, but also record brain activity, activating a recording system at home to collect data from their device. Experimentally, such studies allow tracking of individualized recovery trajectories at the neural level. The study rationale stems from the observation that the brain appears to show an initial reset with first exposure to stimulation, after which it undergoes a slower and more sustained period of relearning and presumably changes in neural plasticity. Clinically, patients need rehabilitation to relearn how to use their brain without depression, which is a process. The experiment hopes to capture the brain changes that mediate these effects. Recovery from depression is ultimately the state of sustained, durable, and meaningful relief from symptoms. Rehabilitation strategies must maximize recovery and provide resilience. Patients must learn the difference between distress and depression, and readouts could assist them in that effort.

With new neurotechnologies, patients should understand that recovery takes more than a stimulator and physicians must manage the therapeutic misconception that the device can do everything, by providing a biologically based reframing of expectations. Researchers must anticipate and manage future unknowns and treat patients as collaborators. All novel interventions must include plans for both good and bad outcomes, include creative and unique trial design for devices, provide long-term stewardship, and plan for when an experiment becomes a treatment.

In conclusion, Dr. Mayberg said that physicians must ask their patients about their experiences and learn from them. Patients can help physicians understand what symptoms are most disabling, which may help physicians ultimately match a patient to an optimal neuromodulation target or method. In turn, physicians can also help patients understand the conditions that they are not treating.

Panel Discussion

Suzanne LeBlang, MD, thanked the presenters for their informative and thought-provoking comments. The question-and-answer session included the following discussion points:

Q. There appears to be heightened desperation for access to new therapies for some vulnerable populations. How should this desperation be managed in clinical trials for new therapeutic devices?

Dr. McDonald. Dr. Mayberg's comment about therapeutic misconception is relevant to managing patient expectations. Expectation management is critical in the early development of any treatment, whether a device or a new pharmaceutical, and is especially difficult for patients with few treatment options. Physicians must continually re-evaluate their patients and reinform them of the experimental nature of a clinical trial. Including patient populations in clinical trial design helps to manage their expectations. Patient involvement and patient engagement during the earliest of stages of developing new treatments is important. Someone who has no hope will look for hope anyway, so there is a tension between taking away hope and managing expectations.

Dr. Mayberg. There is a long history of not-yet-approved treatments for depression, and patients read about the studies. During screening for clinical trials, it can be difficult for a researcher to tell a patient that they are not appropriate for a study. Participants do need to meet the defined criteria. It can also be challenging to tell patients that an experimental treatment may not work. It helps patients to know that physicians are committed to trying new treatments, even if the treatment may not work for a particular patient. Patients "shop around" for clinical trials because there are very few of them. It can feel like an interview. But it is not a negotiation, it is a study.

Dr. Burke. In a clinical trial, it is important to subdue optimism and expectation, which are the core pillars for placebo responses. This is more challenging in clinical practice, because reducing optimism and expectation might make treatment failure more realistic. However, reducing optimism and expectation might reduce some of the placebo effects, which do appear to biologically change the brain. Realizing that additional effect is important, which is why it is controversial.

Dr. Kiss. I completely agree. Many ill people who seek therapy do not receive the therapies in the ways they want them. They do tend to read too much on the internet, and the availability of the information to the public can create a self-selected group that may not be ideal candidates for studies.

Dr. Illes. The clinical ethics world has observed a shift of the pendulum from left to right, and now more to the center, from full-on paternalism two decades ago. The pendulum might swing all the way to consumer-directed care, where patients demand therapies, drugs, interventions, and more based on their new access to the internet and the push toward autonomy. The ethics literature suggests, and the data show, that consumer-

directed intervention is not beneficial to patients. Shared decision-making results in better outcomes for patients than paternalism or public- or patient-directed care.

Dr. LeBlang. With the current advertisements, patients are learning about drugs from television. Sometimes physicians are unaware of all the new drugs that have been approved—or new technologies that are available. Patients can bring these discussions to their doctors and have intelligent conversations; I never cease to learn from my patients. I welcome the knowledge, but I try to keep it in perspective.

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Q. In some places, depression patients are being implanted with stereotactic encephalography (SEEG) electrodes and treated the same as epilepsy patients. How do researchers balance the costs of neuromodulation with the data obtained and with trying to find data that are sufficiently impactful to make a difference in patients' day-to-day lives? For example, how should neuromodulation outcomes be redefined? In some trials, patients are nonresponders and recognize that they are no longer sick. Should that be captured? One question relates to sustainability, and the other is about the risks of not capturing outcomes.

Dr. Mayberg. The patient that I described in my presentation was in remission and could discriminate the moment-to-moment chaos in her life from being ill. Some patients are transformed from who they were but still insist that they are no different. This phenomenon might need to be explained by a philosopher or behavioral neuroscientist. There is no need to chase after a holy grail of which other metric to use. For example, in Parkinson's disease, motor subscales, not the full symptom profile are used to determine whether targeting the lateral subthalamic nucleus is effective for treating motor symptoms. With this disease, outcomes are based on relieving the total depression severity score, not any subset of symptoms, although when DBS for depression is effective, most symptoms improve. Regarding the sustainability of SEEG, on one hand, this approach seems appropriate because it can be a biologically based biomarker; on the other hand, SEEG may be overkill and unneeded. Time and published data will tell. Which biomarker will be the right one? For depression, researchers are still determining which symptom is the most appropriate to direct attention.

Peter Giacobbe, MD, MSc. Physicians tell patients that the goal of treatment is to make them anti-depressed (not to make them happy). Being happy is a different outcome derived from life events and connections. To reestablish homeostasis, physicians can treat the core symptoms and turn off a signal in a neural circuit, but does that ultimately lead to outcomes that are based on happiness? Perhaps that is the role of rehabilitation. Achieving different outcomes requires a different set of interventions.

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Q. Regarding open science, what is the future of neuroscience and modulatory techniques outside of the realm of open access, especially regarding access to patient data? In Canada, there is a big push led by the Montreal Neurological Institute to move away from patents. Will open neuroscience ensure that researchers are seeking maximum benefits and minimized risks for patients?

Ms. Chandler. Some laws already exist to govern neuromodulation techniques. Laws that include a data gathering requirement as a form of oversight are particularly effective. It might be possible to amend all neuromodulation technique laws to include a data gathering requirement

Dr. Illes. PCNEC could take action in this area to impact policymaking for regulatory systems.

Dr. Kiss. A data registry is a great idea and solution, but funding is always a problem. Database administration requires funding that is not available through current channels. However, people are working on this effort, so there is hope.

Dr. Mayberg. For example, the **Tourette Association of American Imaging Consortium** received funding to build a registry, and the NIH Brain Initiative funded a group to establish a master registry of all electrophysiology data. Unfortunately, NIH never mandated that each of its grant awardees bring data into that database. What happens to the data if a registry is not funded indefinitely? What happens to data when researchers retire or leave research? Like-minded people in a small community can choose elements to share and begin the project. A large project can be overwhelming.

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Conclusion

Dr. LeBlang thanked PCNEC for creating a forum to discuss neuroethical issues and to engage with the Focused Ultrasound Foundation community. She also thanked each presenter and panelist, highlighting the value of these interesting and necessary discussions for the field. Dr. Illes and Dr. Lipsman thanked the panelists and attendees for their valuable contributions to the webinar discussion. Dr. Lipsman thanked the Foundation for hosting the webinar, supporting emerging neurotechnology research, and providing a vision for the future. He encouraged attendees to get involved locally and collaboratively on neuroethics issues by helping define priorities, establishing next steps, and visiting the PCNEC website.

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Acknowledgements

PCNEC is a Canadian-led initiative that embraces the international global community of doctors, ethicists, scholars, patients, policymakers, industry, and others. PCNEC is interested in learning how it can move the global community forward on the ethical, legal, and social implications of functional neurosurgery.

The neuroethics webinar was planned by Dr. LeBlang, Dr. Foley, Dr. Lipsman, and Dr. Illes, and produced by Paige Rice, John Burns, and Emily Whipple, PhD. This summary was written by Jill W. Roberts, M.S. and copyedited by Nancy Tuvesson. Each presenter reviewed and approved the content from their presentation and their discussion comments. Dr. LeBlang provided final approval of the summary. The link to view the webinar can be found on the Foundation's website.

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Abbreviations

BCI	brain-computer interface
DBS	deep brain stimulation
EULA	end-user license agreement
FDA	US Food and Drug Administration
NPD	neurosurgery for psychiatric devices
PCNEC	Pan-Canadian Neurotechnology Ethics Consortium
SEEG	stereotactic encephalography
TMS	transcranial magnetic stimulation

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